November 7, 2002

Timothy Adams, Ph.D.
Technical Contact
The Flavor and Fragrance High Production Volume Consortia
1620 I Street, N.W.
Suite 925
Washington, D.C. 20006

Dear Dr. Adams:

The Office of Pollution and Toxics is transmitting EPA's comments on the robust summaries and test plan for Bicyclic Terpene Hydrocarbons posted on the ChemRTK HPV Challenge Program Web site on March 8, 2002. I commend The Flavor and Fragrance High Production Volume Consortia for their commitment to the HPV Challenge Program.

The FFHPVC noted in its test plan that four of the six single chemicals in the bicyclic terpene hydrocarbons category are listed by the U.S. Food and Drug Administration as Generally Recognized as Safe (GRAS). Although the FDA-sponsored prenatal developmental toxicity study in rats, mice and hamsters submitted to address reproductive toxicity is inadequate for that endpoint for the purposes of the HPV Challenge Program, FDA publicly available files may contain additional toxicity data to support your submission.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The Flavor and Fragrance High Production Volume Consortia advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenger Submission:
Bicyclic Terpene Hydrocarbons

SUMMARY OF EPA COMMENTS

The sponsor, the Flavor and Fragrance High Production Volume Consortia, submitted a test plan and robust summaries for the Bicyclic Terpene Hydrocarbons category to EPA on February 19, 2002. EPA posted the submission on the Chemical RTK HPV Challenge Web site on March 8, 2002.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. EPA considers the category to be reasonable.

2. Physicochemical Properties and Environmental Fate. The submitter needs to provide measured vapor pressure data for cis-pinane or dihydropinene and a technical discussion on a category read-across approach for the category members with no available measured biodegradation data. Also, EPA recommends that a Level III fugacity calculation be performed on these chemicals rather than the Level I calculations provided.

3. Health Effects. The data submitted for the reproductive toxicity endpoint are inadequate. Unless the submitter can provide the necessary data to address this endpoint, additional testing is necessary for the purposes of the HPV Challenge Program. The submitter also needs to address deficiencies in the robust summaries.

4. Ecological Effects. Adequate data are available for toxicity to fish, aquatic invertebrates and algae for the purposes of the HPV Challenge Program. The submitter needs to provide missing data elements in the robust summaries.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission

EPA COMMENTS ON THE BICYCLIC TERPENE HYDROCARBONS
CHALLENGE SUBMISSION

Category Definition

The chemical category includes six bicyclic terpene hydrocarbons and four mixtures composed primarily of *alpha*- and *beta*-pinene and smaller amounts of other terpene hydrocarbons. The category definition is adequate.

Category Justification

The submitter bases the category on structural similarities among category members and similar pathways of absorption, metabolism and excretion. There is no evidence that any member of the category will be atypical in terms of its chemical behavior, environmental fate or toxicity. EPA considers this justification to be reasonable.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The data provided by the submitter for melting point, boiling point, partition coefficient and water solubility are adequate for the purposes of the HPV Challenge Program.

Vapor Pressure. EPA disagrees with the submitter's proposal to obtain vapor pressure test data for *alpha*-pinene to support estimated vapor pressure values for the other category members. EPA considers an SAR approach unnecessary because measured or extrapolated vapor pressure data exist for the majority of chemicals (including *alpha*-pinene and *beta*-pinene) in this category, with the exception of *cis*-pinane and dihydropinene. Therefore, the submitter needs to provide measured data (following OECD guidelines) for either cis-pinane or dihydropinene to complete the data set for this endpoint.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

Photodegradation and Stability in Water. The submitter's approach to these endpoints is adequate for the purposes of the HPV Challenge Program.

Biodegradation. The submitter provided adequate data demonstrating varying rates of biodegradation for alpha-pinene, camphene and turpentine gum. However, no experimental data were provided for other members of the category and the BIOWIN estimates provided are not acceptable data for this endpoint. Based on the structural and physical similarities of bicyclic terpene hydrocarbon category members, these substances are also expected to biodegrade in the environment. The submitter needs to include in the test plan and robust summaries a technical discussion of a category read-across approach for those bicyclic terpene hydrocarbon category members with no available measured biodegradation data.

Transport and Distribution (Fugacity). A Level III fugacity calculation should be performed on these chemicals rather than the Level I calculations provided. Although EPA had previously recommended the use of Level I, Level III modeling provides a more rigorous level of analysis.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available for acute, repeated-dose, genetic, and developmental toxicity endpoints for the purposes of the HPV Challenge Program. The data submitted for the reproductive toxicity endpoint are inadequate. The submitter also needs to address deficiencies in the robust summaries.

Reproductive Toxicity. The three submitted studies by Morgareidge (1973a, 1973b, 1973c) are prenatal developmental toxicity studies rather than one-generation reproductive toxicity studies and therefore do not adequately address the reproductive toxicity endpoint. Although the reproductive toxicity endpoint can be addressed by documentation of the evaluation of reproductive organs in an existing 90-day repeated-dose toxicity study and an adequate developmental toxicity study, the data for all submitted 90-day repeated-dose toxicity

studies are not reliable (submitter's assignment of Reliability Code 3). Therefore, EPA believes that the available information is inadequate to address this endpoint and that additional testing is necessary.

Developmental Toxicity. The submitted study by Hoechst AG (1992) was conducted according to OECD Guideline 414 and was given a reliability rating of 1. A supporting developmental toxicity study in rats with a terpene mixture was also submitted. Taken together, the data are adequate for the purposes of the HPV Challenge Program for this endpoint.

Ecological Effects (fish, invertebrates, algal toxicity)

Adequate data from three fish and two invertebrate toxicity tests are available to represent the category for these endpoints.

Algae. EPA considers three of the four submitted algal studies inadequate and the fourth to be of limited value. However, the ECOSAR evaluations provided by the submitter are adequate for the purposes of the HPV Challenge Program.

Specific Comments on the Robust Summaries

Environmental Fate.

Transport and Distribution (Fugacity). The submitter needs to include in the robust summaries all data input values used for modeling estimations. (See Guidance for Robust Summary preparation.)

Health Effects.

Acute Toxicity. Information missing from the robust summaries includes: purity of the test chemical(s), age and body weight of the test animals, duration of observation period, and method for calculating toxicity values.

Repeated-Dose Toxicity. In the 28-day (Hoechst AG 1991) study, the submitter needs to provide information on purity of test substance, frequency of data collection (for clinical signs, body weight, and food and water intake), specific hematology, clinical chemistry and urinalysis parameters examined, organs weighed and examined histopathologically, and statistical methods.

Genetic Toxicity. Missing information for the Ames test on *alpha*-pinene (Jagannath, 1984) and *beta*-pinene (DeGraff, 1983) includes: purity of test chemical, number of replicates/concentration (*beta*-pinene), criteria for positive and negative results, and number of metaphases per concentration examined. Missing details in the *in vivo* mouse micronucleus assay on camphene include: purity of test chemical, information on positive controls, number of cells examined, duration of exposure, and criteria for evaluating results.

Developmental Toxicity. The following details are missing from the OECD TG 414 study robust summary: purity of test chemical, fetal endpoints examined, and maternal LOAEL.

Ecological Effects.

Fish. The submitter needs to provide the following information for the reported EC50 values of 0.18 (CAS No. 80-56-8), 0.50 (CAS No. 127-91-3), and LC50 value of 0.72 mg/L (CAS No. 79-92-5): whether the EC50 and LC50 values are based on measured or nominal concentrations; control mortalities; age of fish at test initiation; pH, dissolved oxygen, and temperature readings throughout tests; statistical tests used and 95% confidence intervals for the LC50.

Invertebrates. The submitter needs to provide the following information for the reported EC50 values of 1.44 (CAS No. 80-56-8) 1.25 mg/L (CAS No. 127-91-3): method used to prepare the test concentrations; statistical

tests use, and resulting 95% confidence intervals; age of the daphnids at test initiation; and ranges for the dissolved oxygen, pH, and temperature readings throughout tests.

Algae. The submitter needs to provide the following information for the reported EC50 value of 1.44 mg/L (CAS No. 127-91-3): water temperature, water hardness, dissolved oxygen, pH, statistical results, and chemical purity.

Followup Activities

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.